

## CLAIMS

That which is claimed is:

1. A method for detecting nucleic acid sequences in two or more collections of nucleic acid molecules, the method comprising:

(a) providing an array of modified polynucleotides bound to a solid surface, each said modified polynucleotide comprising a determinable nucleic acid;

(b) contacting the array of modified polynucleotides with a first collection of labeled nucleic acid comprising a sequence substantially complementary to a nucleic acid of said array, and detecting hybridization of the first collection of labeled complementary nucleic acids to nucleic acids of said arrays;

(c) removing said hybridized nucleic acids;

(d) contacting said array with a second collection of labeled nucleic acid comprising a sequence substantially complementary to a modified polynucleotide of said array; and

(e) detecting hybridization of the first and second labeled complementary nucleic acids to nucleic acids of said arrays;

wherein the modified oligonucleotides are characterized by a pH stability of at least one hour at 37 C at a pH in a range of about 0.5 to 6 and a nuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same sequence and number of bases.

2. The method of claim 1, wherein the first and second collections of nucleic acids are differentially labeled.

3. The method of claim 1, wherein the first and second collections of nucleic acids comprise the same detectable label.

4. The method of claim 1, wherein the step of removing said hybridized nucleic acids comprises incubation of the array with pH 1-2 acid solution.

5. The method of claim 1, wherein the step of removing said hybridized nucleic acids comprises incubation of the array with nuclease.

6. A method of identifying nucleotide differences between the sequence of a target nucleic acid and the sequence of a reference nucleic acid comprising:

a) providing a substrate comprising different modified polynucleotide probes of known sequence at known locations;

b) contacting the target nucleic acid with the modified polynucleotide probes attached to the substrate under conditions for high specificity complementary hybridization;

c) determining which modified polynucleotide probes have hybridized with the target nucleic acid;

d) removing hybridized target nucleic acid from the polynucleotide probes;

e) contacting the reference nucleic acid with the modified polynucleotide probes attached to the substrate under conditions for high specificity complementary hybridization; and

f) comparing the sequence of the reference nucleic acid with the sequences of the modified polynucleotide probes that have hybridized with the target nucleic acid and to identify the nucleotide differences between the sequence of the target nucleic acid and the sequence of the reference nucleic acid.

7. The method of claim 6, wherein each of the different modified polynucleotide probes is attached to the surface of the substrate in a different predefined region.

8. The method of claim 7, wherein each of the modified polynucleotide probes in a predefined region has a different determinable sequence, and further wherein each probe is at least 4 nucleotides in length.

5 further wherein the modified oligonucleotides are characterized by a characteristic selected from the group consisting of (a) a binding affinity of at least about 1.25 times that of a corresponding, non-modified oligonucleotide, (b) a pH stability of at least one hour at 37 C at a pH in a range of about 0.5 to 10; and (c) a nuclease resistance of at least twice that of a naturally occurring oligonucleotide having the same sequence and number of bases.

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